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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,839	LAMBETH ET AL.	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-18 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, Claims 1-6, 9-17 and 26, drawn to a transgenic non-human animal comprising the sequence of SEQ ID NO: 1, a cell or cell line derived from said animal and a method of using said animal and species election of the tissue-specific promoter CX1, in the reply filed on 7/1/04 is acknowledged. The traversal is on the ground(s) that the restriction attempts to impose limitations on the claims because rejoinder of the groups such that groups are directed to a transgenic animal and a vector with an election of species for the transgene would not present an undue burden of search for the examiner and further, groups that were restricted wee in the same class/subclass. This is not found persuasive. Whereas groups I-VIII are in the same class/subclass and groups IX-XV are in the same class/subclass. Further, such classes and subclasses are broad and contain inventions that are not related and are patentably distinct. For example, every transgenic animal would be grouped in 800/8, but this does not indicate that all the transgenic animals are the same invention. The inventions of the groups are patentably distinct because they are directed to compositions comprising non-human transgenic animals and vectors comprising transgenes that would encode proteins with different physical structure, function and utilities. Therefore, because the inventions are different, each from the other, they are

patentably distinct and will require a separate search in the patent and non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 7-8 and 19-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/1/04.

3. Examiner acknowledges Applicant's note in the reply filed on 7/1/04 that Claim 18 was not included in any of the 15 groups of claims. Examiner notes that Claim 18 should have been included in Group I. Group I therefore encompasses claims 1-6, 9-18 and 26.

4. Claims 1-6, 9-18 and 26 are under consideration in the instant application.

Claim Objections

Claim 5 is objected to because of the following informalities: The claim is directed to SEQ ID NOs that have not been elected and therefore contains non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-6 and 9-18 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

When determining whether an applicant has described the utility of invention, one has to determine whether the applicant has described a well-established utility. If not, has the applicant made any assertion of specific, substantial and credible utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for use. In contrast to general utility, a specific utility will be specific to the claimed subject matter. A substantial utility defines a real world utility of the invention and utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context use are not substantial utility (see utility guidelines, in Federal Register January 5, 2001, Volume 66, Number 5, Pages 1092-1099).

Claims 1-6 and 9-18 are directed to a transgenic non-human animal having cells comprising a transgene encoding NADPH oxidase enzyme (NOX) or dual oxidase enzyme (DUOX) wherein the transgene comprises SEQ ID NO: 1 wherein said transgene is operably linked to a tissue-specific promoter wherein said promoter is CX1

wherein said transgene is operably linked to a LoxP flox stop cassette and further comprises a green enhanced fluorescent protein and a method for identifying a therapeutic agent for use in treating inflammation comprising said non-human transgenic animal.

It is noted that the specification does not clearly assert what is the utility of the claimed invention. The disclosure discusses construction of a transgenic mouse comprising human full-length cDNA of NOXI (SEQ ID NO: 1). (page 26, lines 17-30). The authors further disclose an intended use for said transgenic mouse, "to increase expression, or development of a particular disease or condition," wherein a mouse overexpressing Nox1, "can be further crossed with mice that have a proclivity to particular disease states." (page 20, lines 3-8) A working example taught by the authors use Cre/NOX1/Min crossed mice to show that pathogenic challenge with *Citrobacter rodentium* bacteria increased the hyperplastic response of epithelium cells in the colon.

Whereas the claimed invention of the instant application is a transgenic mouse having cells comprising a transgene encoding a NADPH oxidase enzyme or dual oxidase enzyme, the authors do not clearly assert a specific and substantial utility for said mouse. First, the disclosure does not teach a phenotype for a Nox1 mouse. Second, whereas the intended use cited by the specification for said mouse is for crossing with other mice "having a proclivity to particular disease states in order to increase expression or development of a particular disease," this asserted utility is not specific. If a Nox1 mouse is bred with any other transgenic mouse, a skilled artisan

could not predict the phenotype of such a cross. It is well known in the art that transgenesis of mice, especially in terms of expectant phenotypes, is unpredictable. Wherein a predictable phenotype could not be attributed to a Nox1 mouse bred with any other mouse, no known function or utility could be attributed to said mouse such that a skilled artisan would not know how to differentiate, or what functional assay could be used to differentiate, any Nox1 mouse from, for example, any Nox1/SCID mouse. Therefore, because the intended use of the claimed invention, a Nox1 mouse, is to cross said mouse with any mouse such that progeny lacks a predictable phenotype, said mouse has no specific function or utility.

Further, the asserted utility is not substantial. First, the colonic crypt depth effect range for transgenic mice comprising Nox1 challenged with *Citrobacter rodentium* overlap with the colonic crypt depth effect range for NOX1/Min mice similarly challenged. The specification teaches that Nox1 mice given a bacterial challenge show colon crypt depth ranging from ~225-350 microns whereas the NOX1/Min crossed mice given a bacterial challenge show colon crypt death ranging from ~250-450 microns (Figure 4). The phenotype of increased hyperplasia in the colon found in NOX1/Min mice was not substantially different from the phenotype of increased hyperplasia in the colon found in Min mice alone. For example, a Min mouse challenged with bacteria showing colon crypt depth at the higher end of the colonic crypt depth scale taught by the instant specification, or ~350 microns, is not phenotypically different from a NOX1/Min mouse challenged with bacteria showing colon crypt depth in the middle of the colonic crypt depth scale taught by the instant specification, or ~350 microns. As

such, a skilled artisan could not phenotypically differentiate every NOX1/Min mouse from every Min mouse. Second, no other phenotype is shown to be affected with the cross of Nox1 transgenic mice with Min. For example, the instant specification does not teach that crossing Nox1 transgenic mice with Min transgenic mice causes any additional cancerous phenotype such as wasting, increased colonic lesions, or increased white blood cell count. The specification does not support a specific utility because of the lack of an attributable phenotype for a NOX1 transgenic mouse and the lack of a predictable phenotype for a NOX1 transgenic mouse crossed with any genetically altered mouse that is due to the unpredictability of mouse transgenesis. Further, it is not considered to support a substantial utility because of the lack of substantially increased effect of bacterial challenge on NOX1/Min mice versus NOX1 mice.

Therefore, since the authors do not teach a phenotype for a transgenic mouse overexpressing Nox1, a predictable phenotype for Nox1 mice crossed with any other mice, or a predictably "increased expression, or development of a particular disease condition," in Nox1 mice crossed with Min mice, a specific and substantial utility is not supported for the intended use of the claimed invention.

Additionally, if a transgenic non-human animal is deemed to have no specific or substantial utility due to lack of an attributable phenotype, then a cell or cell line derived from said transgenic animal is also without a specific or substantial utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-6 and 9-18 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 1-6 and 9-18 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of

working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims encompass

1) any transgenic non-human animal having cells comprising a transgene encoding any NADPH oxidase enzyme or any dual oxidase enzyme

2) wherein said animal is heterozygous or homozygous for said transgene

3) wherein said transgene is linked to any tissue-specific promoter

4) and a method for identifying a therapeutic agent for use in treating inflammation comprising administering an inflammatory compound to any non-human transgenic animal comprising a transgene encoding any NADPH oxidase enzyme or any dual oxidase enzyme.

Wherein the nature of the invention is a transgenic non-human animal comprising cells expressing either a NADPH oxidase enzyme or a dual oxidase enzyme, neither the specification nor art provide sufficient guidance to make and use the full embodiment of the claimed invention.

In regards to 1) any transgenic non-human animal having cells comprising a transgene encoding any NADPH oxidase enzyme or dual oxidase enzyme 2) wherein said animal is heterozygous or homozygous for said transgene, the specification does not provide sufficient guidance to make any transgenic non-human animal other than mouse having cells comprising a transgene encoding any NADPH oxidase enzyme or dual oxidase enzyme other than Nox1. First, whereas the specification provides sufficient guidance to make a homozygous transgenic mouse having cells comprising a transgene encoding Nox1, the disclosure does not teach how to make any transgenic animal other than mouse having cells comprising a transgene encoding Nox1. As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors. Cameron (Cameron ER Molecular Biotechnology 7:253-276, 1997) noted, "Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying

different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

Hammer et al. (Hammer RE et al. Cell 63 :1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rat demonstrated the most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in a widely different phenotypic response even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been function in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a predictable phenotype.

Further, the specification does not teach a phenotype attributable to said mouse and therefore, a skilled artisan would not know how to use said mouse. Without an attributable phenotype, the function and utility of the claimed invention is unknown. Without a known function and utility for said mouse, it would take an undue burden of

experimentation for a skilled artisan to determine how to use a Nox1 mouse that is lacking an attributable phenotype.

Further, whereas the specification teaches a transgenic mouse having cells expressing NOX1, the specification does not provide sufficient guidance such that a skilled artisan could make and use any transgenic animal having cells expressing any NADPH oxidase enzyme or any dual oxidase enzyme. Wherein the homologues of the NADPH oxidase enzyme encompass Nox1-Nox5, Cheng et al. (Gene 269: 131-140, 2001) teach that tissue expression of these enzymes are variable and that expression of these enzymes in tumor cells are variable as well. The authors teach Nox3 expression to be primarily in fetal tissue, Nox4 is expressed in fetal tissue, kidney, placenta and glioblastoma cells and Nox5 is expressed in fetal tissue, adult spleen and uterus (pages 136-139, see Section 3.3. Tissue expression of Nox3, Nox4 and Nox5 mRNA). Further, the authors teach that individual expression of the Nox homologues were variable in tumor cell lines (page 139, see Section 3.4. Expression of Nox3, Nox4, and Nox5 RNA in cancer cells). Similarly, Edens et al. (J Cell Bio 154(4): 879-891, 2001) teach expression of Duox to be primarily in lung and thyroid. Therefore, wherein tissue and pathological expression of NOX homologs are found to be variable, transgenic non-human animals having cells comprising Nox3, Nox4, or Duox1 would not predictably have the phenotypes of NOX1 transgenic mice taught in the instant specification. Further, whereas the crossing of Nox1 transgenic mouse with any mouse having a proclivity for a disease state provides for progeny of unpredictable phenotype, crossing a transgenic mouse comprising a transgene encoding any NADPH or Duox enzyme

would similarly have an unpredictable phenotype. Without an attributable phenotype, it would take an undue burden of experimentation on a skilled artisan to determine how to use such a mouse.

Finally, in regards to a transgenic non-human animal having cells comprising a transgene encoding NOX or DUOX wherein 3) said transgene is operably linked to a tissue specific promoter, neither the specification nor the art of record provides sufficient guidance to make and use the full scope of the claimed genus, any tissue specific promoter. Whereas the instant specification teaches a transgenic mouse having cells comprising a transgene encoding NOX1, which has been cloned into a target recombining site sequence recognized by the bacterial *Cre* recombinase comprising a nuclear localization signal from SV40, the specification does not teach a transgene encoding NOX or DUOX operably linked to any tissue specific promoter. Whereas the instant specification generally discloses the albumin, lymphoid, T cell receptor, immunoglobulin, neuron, pancreas, cardiac and mammary gland-specific promoters, a skilled artisan is not provided any specific guidance to make or use a transgenic non-human animal having cells comprising a transgene encoding NOX or DUOX operably linked to any of these disclosed promoters. As discussed earlier, the art of promoters in transgenesis is unpredictable. For example, Cowan et al. (Xenotransplant 10:223-231, 2003) teach endothelial targeting in mice and pigs using endothelial specific promoters generate differential phenotypes between the two species of animals. "The ICAM-2 promoter produced tissue-specific hCRP expression, at up to 14-fold the corresponding human level, in 27% of transgenic mice. In contrast, weak transgene expression was

detected in less than 4% of pigs containing intact ICAM-2 promoter constructs." (page 229, paragraph 3) The authors conclude that, "it is clear that although transgenic mice provide some information regarding promoter activity in vivo, making transgenic pigs is the only certain way of assessing candidate tissue-specific promoters." (page 230, paragraph 2) Further, the instant specification provides no guidance for a skilled artisan to make and/or use a NOX1 transgenic non-human animal wherein NOX1 is operably linked to CX1. The instant specification does not provide guidance for a skilled artisan to make and or use a DUOX transgenic non-human animal wherein DUOX transgene is operably linked to CX1. Weber et al. (J Neurosci 18(14): 5264-5274) only teaches the use of the CX1 transcription-binding site to drive promoter activity in neurons from developing cerebral cortex but not in several other cell types. In view of this, an artisan would not be able to predict whether a transgenic mouse could be produced using a CX1 promoter. Therefore, a skilled artisan is not given sufficient guidance from the either the specification and the art to make and/or use a transgenic non-human animal having cells comprising a transgene encoding NOX or DUOX wherein said transgene is operably linked to any tissue specific promoter other than SV40 and is therefore not enabled for the full embodiment of the claimed invention.

In view of the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use any transgenic non-human animal having cells comprising a transgene encoding any NADPH or any DUOX enzyme operably linked to any tissue-specific promoter.

In regards to 4) and a method for identifying a therapeutic agent for use in treating inflammation comprising administering an inflammatory compound to a non-human transgenic animal comprising a transgene encoding a NADPH oxidase enzyme or dual oxidase enzyme, a skilled artisan is not enabled for to make and/or use the claimed method. While, the instant specification teaches a method comprising transgenic mice having cells comprising a transgene encoding NOX1 wherein said transgene is operably linked to SV40 (NOX1 mouse) wherein said mouse is cross-bred to make a NOX1/Min mouse wherein NOX1 mice and NOX1/Min mice are challenged with *Citrobacter rodentium* and colon crypt depth is measured as a function of colonic epithelium hyperplasia wherein bacterial exposure in NOX1/Min mice cause greater hyperplasia than in NOX1 or Min mice, (page 32, Example 11) the instant specification does not teach a method using a NOX1 mouse for the claimed method. It is reiterated that NOX1 mice were normal and did not show any inflammation or other abnormalities. If so, how could an artisan use a mouse that did not have any inflammation for screening anti-inflammatory drugs.

Stedman's Medical Dictionary (27th edition) defines hyperplasia as, "an increase in number of normal cells in a tissue or organ, excluding tumor formation, whereby the bulk of the part or organ may be increased." Inflammation, in the same reference, is defined as, "a fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including: the local reactions and resulting morphologic changes, the

destruction or removal of the injurious material, and the responses that lead to repair and healing." If the model animal did not have any such symptoms, how could the animal be used for screening/identifying drugs that treat these symptoms? Additionally, if the mouse did not have symptoms of colonic hyperplasia, how could the animal be used for screening/identifying drugs that treat hyperplasia in the colon? Therefore, the two conditions are not similar and guidance for one would not anticipate guidance for the other. While the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art, an artisan would require specific guidance to carry out the full breadth of the claimed invention. Whereas the claimed invention is directed to a method comprising inflammation in the colon, the specification teaches a method comprising hyperplasia in the colon and therefore the instant specification does not provide sufficient guidance to a skilled artisan to make and/or use said method for identifying a therapeutic agent for use in treating inflammation.

In view of the lack of guidance provided by the specification, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use a method of using said animal for identifying a therapeutic agent comprising administering an inflammatory compound to said transgenic animal.

11. Claims 1-6 and 9-18 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The non-human transgenic animal and method of using said animal of these claim(s) are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses a non-human animal having cells comprising a transgene encoding NOX or DUOX operably linked to a tissue-specific promoter wherein the transgene is operably linked to a LoxP flox stop cassette further comprising a marker and a method for using said animal comprising administering to said animal an inflammatory agent.

The specification teaches a transgenic mouse produced by pronuclear injection of a vector comprising human full-length cDNA of NOX1 and generation of two lines of NOX1 mice. (page 26, Example 1) Whereas the NOX1 mice did not exhibit a phenotype, Southern Blot analysis of tail snips showed one NOX1 mouse contained one copy of NOX1, while another contained 20 copies of NOX1. (pages 27-28, Example 2) Whereas the specification further describes cross breeding of NOX1 mice with Cre mice, the specification does not describe a predictable phenotype for NOX1/Cre mice. (page 28, Example 3) Whereas the specification describes cross breeding of NOX1/Cre mice with multiple intestinal neoplasia (Min) mice (page 20, lines 3-21), the specification does not describe a predictable phenotype for NOX1/Min mice other than a slight increase in neoplasia of the colon after challenge with *Citrobacter rodentium* as compared to NOX1/Cre mice and Min mice. (page 32, Example 11) The specification

does not teach the physical structure or special characteristics of any animal other than mouse having cells comprising any NADPH or DUOX enzyme other than Nox1 operably linked to any tissue specific promoter other than SV40 and does not teach what are the characteristics of any nonhuman animal having cells comprising any NADPH or DUOX enzyme operably linked to any tissue specific promoter other than a transgenic mouse having cells comprising Nox1 operably linked to SV40.

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the animals resulting from altering the genotype have been described. In the instant case, the claimed invention encompasses any nonhuman mammal comprising any NADPH or DUOX transgene operably linked to any tissue specific promoter. Considering the fact that the claimed invention encompasses transgenic animals as well as non-transgenic animals, and there is no description of the phenotype of the mouse, the phenotype(s) of the claimed animals cannot be predicted because the art of making transgenic animals is highly unpredictable. Wood (Comparative Medicine 5(1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research . . . A specific phenotype is usually expected from genetically altered mice whether they are

transgenic over-expresion models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

Hammer et al. (Hammer RE et al. Cell 63 :1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rat demonstrated the most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in a widely different phenotypic response even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. In line with this, the instant specification further does not describe a transgenic non-human animal comprising any NOX or DUOX enzyme transgene linked to any tissue specific promoter. Based on the description of a transgenic mouse comprising a NOX1 enzyme transgene linked to SV40, a skilled artisan could not envision the physical composition, functional attribute

or utility of a transgenic non-human animal comprising any NOX or DUOX enzyme transgene linked to any specific promoter.

This clearly indicates that the phenotype of a transgenic mouse or rat or any animal having cells comprising any NADPH or DUOX enzyme operably linked to any tissue specific promoter cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genera.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant application, what would have been the result of expressing any NADPH or DUOX enzyme driven by any tissue specific promoter in any nonhuman animal could not be predicted. With the limited information disclosed in the specification, an artisan would have not been able to predict whether the animals would have had the same or different phenotypes compared to the transgenic mouse. In the absence of sufficient description for the animals, the cells derived from the animals also lack sufficient description.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a transgenic non-human animal having cells comprising a transgene encoding a NOX or DUOX enzyme wherein said transgene is linked to a tissue-specific promoter, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is directed to a method for identifying a therapeutic agent for use in treating inflammation. The metes and bounds of the term "inflammation" is not clear because the specification does not described what is encompassed by the term.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh et al. (Nature 401: 79-82, 1999) as applied to the claims above, and further in view of Capecchi et al. (TIG 5(3): 70-76).

The claims are directed to a transgenic non-human animal having cells comprising a transgene encoding NADPH oxidase enzyme or dual oxidase enzyme wherein the transgene comprises SEQ ID NO: 1 wherein said transgene is operably linked to a tissue-specific promoter.

Suh et al. teach the cloning of mox1 (later renamed to NOX1 and having 99.8% homology with SEQ ID NO: 1), which encodes a homologue of the catalytic subunit of the superoxide-generating NADPH oxidase. The authors teach that mox1 was expressed most in colon and that the colon-carcinoma cell line Caco-2 expressed large quantities of mox1 message (page 80, paragraph 2). Further, the authors teach that mox1-transfected NIH 3T3 cells grown in culture take on a transformed appearance, becoming elongated and losing contact inhibition (page 81, paragraph 2) and mox1-transfected cells produced aggressive tumors in athymic mice (page 81, paragraph 3). The authors conclude that Mox1 may participate in disregulated growth in

hyperproliferative disorders such as cancer and atherosclerosis. The authors do not teach a transgenic mouse comprising a transgene encoding Nox1.

Capecchi et al. teach that through gene targeting, "the potential now exists to generate mice of any desired genotype. The experimenter chooses both which gene to mutate and how to mutate it." (page 70, paragraph 3). The authors further teach a method for generating genetically manipulated mice utilizing mouse embryonic stem cells.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the method of Capecchi et al. to generate a transgenic mouse with the NOX1 transgene taught by Suh et al. with a reasonable expectation of success. An artisan would have had a reasonable expectation of success because Capecchi et al. teach a method of generating a genetically altered mouse using mouse embryonic cells comprising a gene and Suh et al. teach the nucleic acid sequence of NOX1 and the cloned DNA. An artisan would have been motivated to modify the method of Capecchi et al. to generate a mouse comprising a genetically altered mouse having cells comprising the NOX1 transgene taught by Suh et al. because doing so would provide a mouse model for hyperproliferative disorders such as cancer and atherosclerosis and "such models should prove useful for analyzing the pathology of the disease as well as providing systems for exploration of new therapeutic protocols, including gene therapy" for thyroid disorders, (Capecchi et al. page 76, paragraph 2) particularly in view of the possible role of NOX1 in colon cancer as evidenced by the study of Suh et al.

14. Claims 1-4 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dupuy et al. (J Biol Chem 274(52): 37265-37269) as applied to the claims above, and further in view of Capecchi et al. (TIG 5(3): 70-76).

The claims are directed to a transgenic non-human animal having cells comprising a transgene encoding NADPH oxidase enzyme or dual oxidase enzyme wherein the transgene comprises SEQ ID NO: 1 wherein said transgene is operably linked to a tissue-specific promoter.

Dupuy et al. teach purification and cloning of porcine and human $p138^{tox}$ (Duox) found in thyroid plasma membrane and designate the protein the main, if not the sole, component of the thyroid NADPH oxidase. The authors further show localization of the gene in the human genome and describe specific structural features that account for its biochemical properties such as calcium binding EG-hand motifs. The authors conclude that the cloning and structural characterization of this gene is relevant because it is a new marker of thyrocytes and could be relevant in thyroid disorders. The authors do not teach how to generate a transgenic animal expressing DUOX.

Capecchi et al. teach that through gene targeting, "the potential now exists to generate mice of any desired genotype. The experimenter chooses both which gene to mutate and how to mutate it." (page 70, paragraph 3). The authors further teach the method taught in the instant specification of generating genetically manipulated mice utilizing mouse embryonic stem cells.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the method of Capecchi et al. to generate a transgenic mouse with the

transgene of the DUOX enzyme taught by Dupuy et al. with a reasonable expectation of success. An artisan would have had a reasonable expectation of success because Capecchi et al. teach a method of generating a genetically altered mouse using mouse embryonic cells comprising a gene and Dupuy et al. teach the cloning of the DUOX enzyme transgene. An artisan would have been motivated to modify the method of Capecchi et al. to generate a mouse comprising a genetically altered mouse having cells comprising the DUOX transgene taught by Dupuy et al. because doing so would provide a mouse model for thyroid disorders since DUOX enzymes were shown to be the thyroid specific and a marker of thyrocyte differentiation. (Dupuy et al., page 37268-37269, Figures 4 and 5) and "such models should prove useful for analyzing the pathology of the disease as well as providing systems for exploration of new therapeutic protocols, including gene therapy" for thyroid disorders. (Capecchi et al. page 76, paragraph 2).

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NCA

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